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Regional gray matter atrophy in relapsing remitting multiple sclerosis: Baseline analysis of multi-center data

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Abstract
Regional gray matter (GM) atrophy in multiple sclerosis (MS) at disease onset and its temporal variation can provide objective information regarding disease evolution. An automated pipeline for estimating atrophy of various GM structures was developed using tensor based morphometry (TBM) and implemented on a multi-center sub-cohort of 1008 relapsing remitting MS (RRMS) patients enrolled in a Phase 3 clinical trial. Four hundred age and gender matched healthy controls were used for comparison. Using the analysis of covariance, atrophy differences between MS patients and healthy controls were assessed on a voxel-by-voxel analysis. Regional GM atrophy was observed in a number of deep GM structures that included thalamus, caudate nucleus, putamen, and cortical GM regions. General linear regression analysis was performed to analyze the effects of age, gender, and scanner field strength, and imaging sequence on the regional atrophy. Correlations between regional GM volumes and expanded disability status scale (EDSS) scores, disease duration (DD), T2 lesion load (T2 LL), T1 lesion load (T1 LL), and normalized cerebrospinal fluid (nCSF) were analyzed using Pearson's correlation coefficient. Thalamic atrophy observed in MS patients compared to healthy controls remained consistent within subgroups based on gender and scanner field strength. Weak correlations between

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thalamic volume and EDSS ($r=-0.133$; $p<0.001$) and DD ($r=-0.098$; $p=0.003$) were observed. Of all the structures, thalamic volume moderately correlated with T2 LL ($r=-0.492$; P-value<0.001), T1 LL ($r=-0.473$; P-value<0.001) and nCSF ($r=-0.367$; P-value<0.001).

1. Introduction

Multiple sclerosis (MS) is the most common demyelinating disorder of the human central nervous system. White matter (WM) and gray matter (GM) atrophy and the presence of demyelinating lesions are hallmarks of MS. (Bermel et al., 2003; Cifelli et al., 2002; Ge et al., 2007; Inglese et al., 2007; Henry et al., 2008; Riccitelli et al., 2012; Sharma et al., 2006; Wylezinska et al., 2003). Based on histopathology, atrophy is thought to reflect demyelination, axonal and neuronal loss that occurs early in the disease, but the precise pathological substrate of cortical atrophy remains unknown (Wegner et al., 2006). Both brain atrophy and lesion load are found to be predictors of long term disability (Di Filippo et al., 2010; Popescu et al., 2013).

Magnetic resonance imaging (MRI) is the most common modality for atrophy quantification and lesion load in MS. A number of studies suggest that regional atrophy is a more sensitive indicator of the disease than global atrophy. Deep GM structures appear to atrophy early on in the disease (Audoin et al., 2010; Bergsland et al., 2012; Charil et al., 2007; Fisher et al., 2008; Fisniku et al., 2008; Mesaros et al., 2008; Pagani et al., 2005; Raz et al., 2010; Sabatini et al., 1996; Sepulcre et al., 2006). Deep GM atrophy is found to correlate with clinical disease markers such as fatigue (Niepel et al., 2006), cognition (Brass et al., 2006; Houtchens et al., 2007; Nocentini et al., 2014), expanded disability status scale (EDSS) score (Bakshi et al., 2001; Prinster et al., 2010; Tao et al., 2009) and MR derived measures such as T2 and T1 lesion loads (Ceccarelli et al., 2009; Tao et al., 2009).

Voxel based morphometry (VBM) is frequently used to assess regional atrophy in MS. Studies using VBM have demonstrated atrophy in various regional GM structures (Ceccarelli et al., 2009; Raz et al., 2010; Bendfeldt et al., 2012). In the VBM analysis, each individual scan is spatially normalized to a common stereotactic space, which is then segmented and smoothed to minimize the image registration errors. Segmented volumes are corrected with their respective Jacobian determinant (JD), which represents the volume change. Optimized VBM was implemented using an unbiased template in the VBM analysis. Prinster et al. (2010) implemented optimized VBM and demonstrated atrophy in various deep and cortical GM in relapsing remitting MS (RRMS). Ceccarelli et al. (2012) compared VBM and optimized VBM, DARTEL (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) in 26 relapsing-remitting MS (RRMS) patients. They also investigated the effect of lesion in-painting prior to segmentation and their results indicate robust atrophy assessment with DARTEL (Ashburner, 2007) when combined with lesion in-painting (Chard et al., 2010).

Tensor based morphometry (TBM) is a technique for investigating disease-related changes in brain structures and is shown to provide methodological improvements over VBM (Hua et al., 2013; Kim et al., 2008). The main advantage of TBM over VBM is that the former does not require tissue segmentation. TBM was implemented to investigate structural changes in schizophrenia (Whitford et al., 2007), traumatic brain injury (Kim et al., 2008), dementia (Brambati et al., 2007, 2009), Alzheimer's disease (Hua et al., 2008a, 2008b, 2013; Leow et al., 2009), HIV/AIDS (Lepore et al., 2008), and pediatric MS (Aubert-Broche et al., 2011). Both VBM and TBM require templates to assess volume changes. Use of an unbiased template to estimate volume changes is shown to be robust against registration errors and improved statistical power (Joshi et al., 2004; Kim et al., 2008; Lepore et al., 2008). An unbiased template can be generated from a group of MRI image volumes using iterative non-linear registration and averaging.

Tao et al. (2009) were the first to implement TBM to estimate regional atrophy in adult RRMS patients. Their results indicated significant atrophy in major regional GM structures that included thalamus, putamen, and caudate nucleus. In that study, the authors reported relatively strong correlation between thalamic atrophy and EDSS and lesion loads. The major limitations of that study were the relatively modest sample size (88 patients), inclusion of patients from a single center, and relatively long disease duration (DD). These limitations also extend to a number of other published studies and limit the generalization of the results. In the present study, we implemented TBM to quantify regional GM atrophy in RRMS patients with relatively short DD. Approximately 91% of patients had DD less than 3 years. These patients were scanned at different centers on different scanners with varying field strengths and manufacturers as part of multi-center clinical trial (Lublin et al., 2013). Such heterogeneity is inevitable in multi-center trials that require large sample size. Multi-center data is critical for identifying MRI-derived measure in evaluating the treatment efficacy and patient management. In this study the regional GM atrophy in MS patients compared to healthy controls was analyzed and the correlation of atrophy with other MRI and clinical scores was estimated on a large cohort. Regional atrophy was estimated using normalized mean JD of the deformation fields obtained following the non-linear symmetric diffeomorphic registration with an unbiased template (Tao et al., 2009; Avants et al., 2008). We implemented lesion in-painting prior to registration since it was shown to improve the VBM analysis (Ceccarelli et al., 2012; Datta et al., 2014).

2. Materials and methods

2.1. Patients

All patients included in this study were recruited in CombiRx, a double-blind randomized clinical trial for evaluating the effects of the combination of two drugs, (interferon beta-1a and glatiramer acetate) compared to treatment with either